MDM2 INHIBITORS AND COMBINATIONS THEREOF

FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to a pharmaceutical combination comprising (a) an Mdm2 inhibitor and (b)(i) a MEK inhibitor and/or (b)(ii) Bcl2 inhibitor, particularly for use in the treatment of a cancer. This disclosure also relates to uses of such combination for preparation of a medicament for the treatment of a cancer; methods of treating a cancer in a subject in need thereof comprising administering to said subject a jointly therapeutically effective amount of said combination; pharmaceutical compositions comprising such combination and commercial packages thereto.

BACKGROUND OF THE DISCLOSURE

[0002] The advent of targeted therapies for cancer has increased patient lifespan for various malignancies and helped to appreciate the complexity of tumors through the study of drug resistance mechanisms. The fact that clinical responses to targeted agents are generally incomplete and/or transient results from a multitude of factors that can be broadly put into two classes: toxicities that prevent optimal dosing of drugs and consequently limit target engagement (Brana and Siu 2012, Chapman, Solit et al. 2014), and the ability of cancers to adapt and maintain their proliferative potential against perturbations (Druker 2008, Chandarlapaty 2012, Doebele, Pilling et al. 2012, Duncan, Whittle et al. 2012, Katayama, Shaw et al. 2012, Lito, Rosen et al. 2013, Sullivan and Flaherty 2013, Solit and Rosen 2014). Combinations of drugs can address both these factors by improving overall efficacies and at the same time targeting tumor robustness and complexity to counter resistance (Robert, Karaszewska et al. 2015, Turner, Ro et al. 2015). It is not yet clear how many drugs are required and which processes need to be targeted in combination to overcome cancer. But it is almost certain that different pathways or drivers need to be inhibited, most likely requiring two or more drugs (Bozic, Reiter et al. 2013). This is supported by the successes of combining conventional chemotherapeutic agents to treat cancers (DeVita 1975), and combination therapies for infectious diseases such as HIV (Porter, Babiker et al. 2003), as well as by theoretic approaches showing how biological robustness can be challenged by increasing the order of perturbations (Lehar, Krueger et al. 2008).

[0003] In spite of numerous treatment options for patients with specific types of cancer, there remains a need for effective and safe combination therapies that can be administered for the effective long-term treatment of cancer.

SUMMARY OF THE DISCLOSURE

[0004] It is an object of the present disclosure to provide for a medicament to improve treatment of a cancer, in particular to improve treatment of cancer through inhibition of cell growth (proliferation) and induction of apoptosis. It is an object of the present disclosure to find novel combination therapies, which selectively synergize in inhibiting proliferation and/or in inducing apoptosis.

[0005] Such inhibitors as MDM2 inhibitors, MEK inhibitors and BCL2 inhibitors, as a monotherapy, demonstrate anti-proliferative (cytostatic) and pro-apoptotic (cytotoxic) activities in vitro and in vivo pre-clinical assays. Surprisingly it has been found that a pharmaceutical combination comprising

[0006] (a) an MDM2 inhibitor selected from (6S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-(propan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one, or a pharmaceutically acceptable salt thereof, and (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one, or a pharmaceutically acceptable salt thereof; and

[0007] (b)

[0008] (i) a MEK inhibitor selected from the group consisting of trametinib, 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide, (S)-5-fluoro-2-(2-fluoro-4-(methylthio)phenylamino)-N-(2-hydroxypropoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide, PD0325901, PD-184352, RDEA119, XL518, AS-701255, AS-701173, AS703026, RDEA436, E6201, R04987655, RG7167, and RG7420 or a pharmaceutically acceptable salt thereof; and/or

[0009] (ii) Bcl2 inhibitor selected from the group consisting of ABT-737, ABT-263 (navitoclax) and ABT-199, or a pharmaceutically acceptable salt thereof,

[0010] has a beneficial synergistic interaction, improved anti-cancer activity, improved anti-proliferative effect, and improved pro-apoptotic effect. These combinations demonstrated a synergistic effect in cell growth inhibition and induction of cell death by apoptosis.

[0011] Further, it has been found that a combination of

[0012] (a) an MDM2 inhibitor selected from (6S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-(propan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one, or a pharmaceutically acceptable salt thereof, and (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one, or a pharmaceutically acceptable salt thereof; and

[0013] (b)

[0014] (i) a MEK inhibitor selected from the group consisting of trametinib, 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide, (S)-5-fluoro-2-(2-fluoro-4-(methylthio)phenylamino)-N-(2-hydroxypropoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide, PD0325901, PD-184352, RDEA119, XL518, AS-701255, AS-701173, AS703026, RDEA436, E6201, R04987655, RG7167, and RG7420 or a pharmaceutically acceptable salt thereof; and/or

[0015] (ii) Bcl2 inhibitor selected from the group consisting of ABT-737, ABT-263 (navitoclax) and ABT-199, or a pharmaceutically acceptable salt thereof,

[0016] may advantageously comprise further inhibitors selected from EGFR inhibitors, PI3K inhibitors and BRAF inhibitors. In addition, CDK4/6 inhibitor or standard of care